

# Usefulness of myocardial performance index in multiple sclerosis mitoxantrone-induced cardiotoxicity

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## ABSTRACT

**Aims** The authors sought to investigate the ability of the Doppler-derived myocardial performance index (MPI) to predict cardiotoxicity in multiple sclerosis (MS) patients under mitoxantrone therapy.

**Methods and results** The authors prospectively evaluated 28 MS patients (mean age  $41 \pm 9$  years, 12 males and 16 females) treated with low-dose mitoxantrone (basal mean cumulative dose  $30 \pm 14$  mg/m<sup>2</sup>, end of follow-up mean dose  $41 \pm 17$  mg/m<sup>2</sup>). All patients underwent two-dimensional and Doppler-echocardiography at baseline and after a mean follow-up of  $22 \pm 8$  months. MPI was estimated using mitral inflow and left ventricular (LV) outflow pattern. Comparing data at baseline and at the end of follow-up, significant decrease in ejection fraction (EF) was observed ( $60 \pm 5$  vs  $56 \pm 4$ ,  $p < 0.03$ ). The MPI was  $0.52 \pm 0.1$  at baseline and  $0.60 \pm 0.1$  at the end of follow-up ( $p < 0.04$ ). Such difference was mainly due to a isovolumic relaxation time prolongation ( $80 \pm 12$  at baseline and  $98 \pm 30$  at the end of follow-up,  $p < 0.05$ ). The area under the receiver operating characteristic curve, analysed for an MPI cut-point value of 0.57, in identifying a significant reduction of LVEF  $\leq 50\%$  was of  $0.94 \pm 0.065$  with sensitivity and specificity of 97.5% and 90%, respectively.

**Conclusion** In conclusion, it can be speculated that a higher basal value of MPI could represent a subclinical LV cardiotoxicity, identifying a future decrease of EF and a progression to congestive heart failure in MS patients under mitoxantrone therapy.

## INTRODUCTION

Mitoxantrone-induced cardiotoxicity is a well-known problem in the treatment of multiple sclerosis (MS) patients that limits the therapeutic use of this agent.<sup>1,2</sup> It may lead to an asymptomatic decrease of left ventricular ejection fraction (LVEF), irreversible cardiomyopathy and ultimately to congestive heart failure. Cardiotoxicity is related to the cumulative dose (CD) of mitoxantrone. However, a temporary, but important decrease in the LVEF, has been reported after only one or two doses of mitoxantrone, and a subset of patients show signs of cardiomyopathy even at low doses.<sup>3</sup> Thus, to optimise mitoxantrone treatment and to prevent cardiac injury, an early detection of cardiotoxicity is needed. Currently, LVEF measurement by echocardiography is the most frequently used noninvasive diagnostic tool for monitoring cardiotoxicity during mitoxantrone treatment,<sup>4</sup> although it represents a late index of myocardial injury, it

depends on certain geometric assumptions, and is significantly influenced by the inter- and intra-observer variability. Tissue Doppler echocardiography is able to detect an early involvement of the systolic myocardial function in this category of patients, but its predictive role is still unknown.<sup>5</sup> On the other hand, several studies demonstrated that diastolic parameters are affected before the systolic indexes.<sup>6–9</sup> In a previous study, we had shown a correlation between Myocardial Performance Index (MPI), a Doppler-derived index including both, diastolic and systolic properties of the left ventricle (LV), and early subclinical variations of LV function in MS patients under mitoxantrone therapy.<sup>10</sup> The MPI has been shown to be independent of heart rate, can be easily obtained and has good reproducibility.<sup>11</sup> Most importantly, it enables integrated analysis of both, systolic and diastolic LV function, and provides prognostic information about morbidity and mortality in many cardiac diseases, even in the absence of clinical signs. However, the diagnostic value of this parameter in the early assessment of preclinical anthracycline cardiotoxicity remains undefined. Starting from the previously mentioned group of MS patients,<sup>10</sup> we therefore, prospectively investigated the modifications of MPI compared with increasing of CD of mitoxantrone, over a period of about 2 years, to focus on the development of cardiotoxicity predictive value of this Doppler index.

## SUBJECTS AND METHODS

### Subjects

Twenty-eight caucasian patients (12 males and 16 females, mean age  $41 \pm 9$  years) affected by MS under mitoxantrone treatment ( $30 \pm 14$  mg/m<sup>2</sup>,  $41 \pm 17$  mg/m<sup>2</sup> were, respectively, the basal and the end of follow-up mean cumulative dose) were followed for  $22 \pm 8$  months at the Operative Unit of Neurology, Hospital of Fidenza, Parma IT. Of the total, 12 patients had relapsing-remitting MS, and 16 had secondary progressive MS. Patients were treated with mitoxantrone IV every 3 months. On every occasion of the treatment, all subjects underwent a 12-lead standard ECG, a clinical examination and a blood pressure evaluation. A complete Doppler echocardiography was periodically evaluated. According to the current recommendations,<sup>4</sup> patients with an LVEF  $< 50\%$  were excluded from mitoxantrone treatment; the treatment is discontinued when the LVEF drops to  $< 50\%$ , or if there are clinical signs of cardiac

dysfunction. If a difference of >10% is found compared with the preceding value, the infusion is not applied. The clinical data at baseline and at the end of follow-up are summarised in table 1. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

### Echocardiography

Conventional and Doppler echocardiography were performed according to the recommendations of the American Society of Echocardiography.<sup>12</sup> All examinations were performed and interpreted by an independent physician (PP) blinded to all patients' characteristics, with a commercially available system (EnVisor CO, Philips Medical Systems, Andover, MA, USA) using a 2.5 MHz transducer. LV dimensions were measured by M-mode using a leading edge-to-edge convention. The measured parameters were represented by: inter-ventricular septal thickness (IVS), posterior wall thickness (PW), end-diastolic LV diameter (LVEDD), end-systolic LV diameter (LVESD), LV relative wall thickness (RWT), end-diastolic and end-systolic LV volume, ejection fraction (EF) and fractional shortening (FS). RWT was calculated as (IVS+PW)/LVEDD. LV mass was assessed using the Penn-convention and indexed to body surface area (LVM/BSA).<sup>13 14</sup> LV end-diastolic and end-systolic volume, as well as EF were calculated according to the biplane Simpson rule. FS was assessed as a percentage ratio: (LVDD-LVDS)/LVDD. EF was considered significantly reduced when it was <50%.

The blood flow across the mitral valve was monitored by the pulse-Doppler technique in the apical 4-chamber view. The sample volume of 3–5 mm was placed at the tip of the valve leaflets with the Doppler beam aligned perpendicular to the plane of the mitral annulus. The blood flow profile contains a diastolic early filling (E) wave and atrial contraction (A) wave in diastole. Mitral inflow E-wave deceleration time, peak velocity (pv) and time velocity integral (tvi) of E and A wave, respectively, and E/A ratios were assessed. Overall LV function was assessed using the MPI, defined as the sum of isovolumetric relaxation and contraction times (IRT and ICT, respectively) divided by the ejection time.<sup>11</sup> LV outflow was recorded at the apical long-axis view with pulsed-wave Doppler, with the sample volume positioned just below the aortic valve. Other aspects of the technique have been previously discussed.<sup>10</sup> Measurements were usually done in triplicate on different heart cycles. In our echocardiographic laboratory, the inter- and intra-observer variability for MPI assessment are 3.1% and 3.4%, respectively.<sup>10</sup>

### Statistics

Data were expressed as mean±SD. The changes from enrolment to the last visit were compared using a two-tailed Student's *t* test for paired data, after ascertaining data compatibility with the normal distribution (Kolmogorov-Smirnov's procedure). The relationship between parameters was evaluated by simple linear regression analysis. Receiver operating characteristic curve (ROC) analysis was generated to test the predictive value of MPI to detect subtle changes in LV myocardial performance in MS patients under mitoxantrone therapy. Values were considered significantly different at *p* value <0.05. Statistical analyses were made using Statistical Package for Social Sciences for Windows, V.15.0 (SPSS Inc.).

## RESULTS

### Baseline characteristics of patients

MS patients were homogeneous for age and BSA. Heart rate, systolic and diastolic blood pressure were similar comparing

**Table 1** Clinical data at baseline and at the follow-up

Parameters	Baseline (n=28)	Follow-up (n=28)
Age (years)	41.4±9.2	43.1±9.7
Sex (male/female)	12/16	12/16
Body surface area (m <sup>2</sup> )	1.84±0.3	1.85±0.3
Mitoxantrone cumulative dosage (mg/m <sup>2</sup> )	30.3±14.5	40.9±17.5
Heart rate (beats/min)	69.9±7.4	71.7±8.0
Systolic blood pressure (mm Hg)	120.0±15.5	119.3±15.2
Diastolic blood pressure (mm Hg)	76.3±10.8	79.3±6.8

Data are expressed as mean±SD.

baseline to the end of follow-up parameters (table 1). At baseline, all the patients were already under mitoxantrone treatment, and the mean cumulative dose was 30±14 mg/m<sup>2</sup> at enrolment, and 41±17 mg/m<sup>2</sup> at the end of follow-up, respectively. At baseline, ECG tracing was substantially normal in all patients. During the follow-up, none of the patients developed signs or symptoms of heart failure, alterations of the electrocardiogram, renal or hepatic dysfunction.

### Standard echocardiography study

Comparing baseline to the end of follow-up echocardiography no significant differences were observed for septum and posterior wall thickness, LV dimensions, relative wall thickness and LVM/BSA (table 2). Mild insufficiency of the mitral and aortic valve were found at the end of follow-up in 12 (43%) and 2 (7%) patients, respectively. A significant EF decrease was observed at the end of follow-up (60.2±4.7 vs 56.3±4.3, *p*<0.03). According to the current recommendations,<sup>4</sup> five patients had earlier interrupted the mitoxantrone therapy for the estimation of an EF ≤50%.

### Doppler measurements

LV diastolic function was similar at baseline and at the end of follow-up (table 3). The MPI increased after mitoxantrone therapy in 22 patients (80%) compared with baseline values. No patients showed a significant decrease of MPI at the end of follow-up. After a mean follow-up period of 22 months, MPI significantly increased (0.52±0.10 vs 60±0.12). This was mainly due to an IRT prolongation (80±12 ms at baseline vs 98±30 ms at the end of follow-up, *p*<0.05) (table 3). Using ROC curve analysis, the MPI yielded an area under the curve of 0.94±0.065. Using an MPI ≥0.57 as the cut-point, a significant reduction of LVEF ≤50% was identified with a sensitivity and specificity of 97.5% and 90%, respectively.

**Table 2** Conventional echocardiographic data at baseline and at the follow-up

Parameters	Baseline	Follow-up	Significance
LV end-diastolic diameter (mm)	47.3±5.5	46.9±5.7	NS
LV end-systolic diameter (mm)	30.0±5.0	29.6±5.1	NS
Septal wall thickness (mm)	9.4±1.3	9.7±1.4	NS
Posterior wall thickness (mm)	8.8±1.2	9.3±1.1	NS
LV fractional shortening (%)	36.1±5.4	30.8±9.2	NS
LV ejection fraction (%)	60.2±4.7	56.3±4.3	<i>p</i> <0.03
LV mass index (gr/m <sup>2</sup> )	92.4±20.0	82.4±15.1	NS
RWT (%)	0.40±0.05	0.39±0.05	NS
LV end-diastolic volume (ml)	87.4±24.8	78.9±16.4	NS

Data are expressed as mean±SD.  
LV, left ventricle.

**Table 3** Summary of Doppler time intervals and mitral flow patterns

Parameters	Baseline	Follow-up	Significance
LV MPI	0.52±0.10	0.60±0.12	p<0.04
LV ICT (ms)	65.4±18.0	62.8±24.5	NS
LV IRT (ms)	80.4±12.0	97.7±30.0	p<0.05
LV ET (ms)	275.7±24.8	276.7±31.3	NS
E-wave deceleration time (ms)	175.3±35.2	171.8±28.3	NS
E <sub>pv</sub> (cm/sec)	62.2±12.4	59.6±12.1	NS
E <sub>tvi</sub> (cm)	9.2±1.8	8.6±1.7	NS
A <sub>pv</sub> (cm/sec)	60.1±15.8	61.3±14.4	NS
A <sub>tvi</sub> (cm)	6.0±2.1	6.1±1.8	NS
E <sub>pv</sub> /A <sub>pv</sub> (cm/sec)	1.1±0.4	1.05±0.4	NS
E <sub>tvi</sub> /A <sub>tvi</sub> (cm)	1.7±0.7	1.6±0.6	NS

Data are expressed as a mean value±SD.

LV, left ventricle; MPI, myocardial performance index; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; ET, ejection time; E, early diastolic filling wave; A, atrial contraction wave; PV, peak velocity; TVI, time-velocity integral.

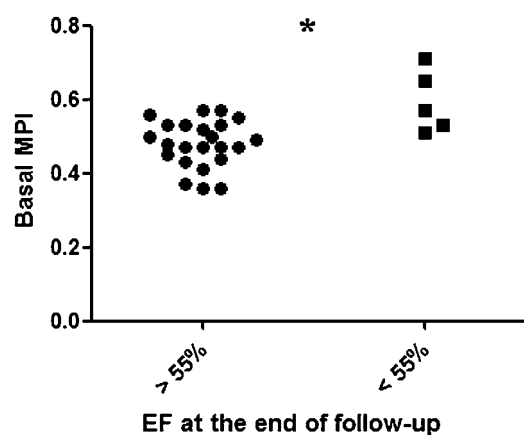
### Correlations

MPI significantly correlated to RWT ( $r=0.45$ ,  $p<0.05$ ), and to mitoxantrone cumulative dose ( $r=0.43$ ,  $p<0.05$ ), as previously demonstrated<sup>10</sup>; conversely, it was independent from heart rate, blood pressure, age, BSA and LVEF.

### DISCUSSION

In the last years, a growing number of young MS patients were treated with mitoxantrone; the derived anthracycline cardiotoxicity might increase the morbidity and mortality risk of these patients. Early detection and treatment of cardiotoxic side-effects could be crucial to prevent further overt heart failure. However, currently, no diagnostic parameter is available allowing ubiquitous, sensitive and specific detection of preclinical anthracycline cardiomyopathy and prediction of prognosis. In a previous study, we examined the MPI in patients with MS receiving mitoxantrone. It appeared to be a sensitive and noninvasive technique for detecting subclinical LV dysfunction, which occurred at a substantially low dose of mitoxantrone, and demonstrated the relationship between cardiotoxicity and CD of mitoxantrone.<sup>10</sup> Previous studies demonstrated that there is association between MPI and other parameters of LV in different cardiac disorders.<sup>15–19</sup> Bruch and colleagues have demonstrated that the MPI could differentiate heart failure patients from a control group among subjects undergoing elective LV catheterisation, with an adequate (>80%) sensitivity and specificity.<sup>15</sup> In addition, MPI was an independent predictor of risk of future heart failure in a population-based cohort of Swedish elderly patients without apparent major cardiac disease.<sup>20</sup> Specifically regarding anthracycline use, Ishii and co-workers have suggested early and significant increases in MPI in patients under chemotherapy, indicating that this index could be predictive of future cardiac dysfunction.<sup>21</sup>

In the present study, we prospectively evaluated the role of the MPI to predict the development of LV cardiotoxicity, expressed as a reduction of LVEF ≤ 50%, in asymptomatic MS patients treated with low to moderate CD of mitoxantrone. This parameter alteration occurred before changes in other conventional echocardiographic measures (table 3). Although we did not observe any overt heart failure in our patients, we found a high value of MPI compared with normal values of EF at enrolment, while at the end of follow-up we recorded a significant decrease in EF and a further increase in MPI (figure 1). Thus, it is likely that cardiotoxicity will occur more often in the future. To optimise mitoxantrone treatment in the individual SM patients, and to prevent cardiac injury, early detection of cardi-



**Figure 1** Comparison between basal MPI and EF at baseline and at the end of follow-up (\* $p<0.04$ ).

otoxicity is needed. In this light, we can speculate that a higher basal value of MPI could represent a subclinical LV cardiotoxicity, identifying a future decrease of EF, and a progression to congestive heart failure. These data are supported by the ROC curve which analysed a significant reduction of LVEF ≤ 50% with an MPI cut-point value of 0.57. Using that cut-point was identified with a sensitivity and specificity of 97.5% and 90%, respectively.

Our data agree with previously mentioned studies<sup>5–8</sup> that demonstrated LV diastolic function to be mainly impaired before systolic function after mitoxantrone therapy. On the other hand, it could be noted that previous studies demonstrated impaired systolic function earlier than diastolic function, and this apparent paradox may be explained by the methodology of analysis used.<sup>4</sup>

Some potential limitations of the current study deserve attention in the data interpretation. First, the study population was relatively small for prognostic considerations. However, the absence of confounding comorbidity, the careful methodology with multiple continuous measures, the peculiarity of the study population and the few published papers regarding this issue, make our work robust enough to counteract this limitation. Second, our patients received mitoxantrone at different doses and intervals. This made our study population less homogenous. Finally, a longer follow-up of these patients could be essential for the possible late cardiotoxicity and to define outcomes.

In conclusion, our data confirm MPI as an index-sensitive, easily obtained, reproducible and noninvasive technique for detecting significant subclinical LV dysfunction, and to predict future cardiotoxicity in MS patients, already at a low to moderate dose of mitoxantrone therapy, than current standard echocardiographic parameters. We expect that MPI may be used as an early and adjunctive parameter for detecting subclinical cardiotoxicity, and for monitoring the impact of treatment of mitoxantrone in MS patients.

**Contributors** All the authors.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** The local medical ethics committee.

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